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Wellstat Management Company. LLC
LEGAL DEPARTMENT
930 CLOPPER ROAD
GAITHERSBURG, MD 20878

EXAMINER	
ZEMAN, ROBERT A	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/743,649	BELL ET AL.	
	Examiner	Art Unit	
	ROBERT A. ZEMAN	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,7,9-15 and 17-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,7,9-15 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-18-06, 6-6-07 (2), 1-7-08 and 3-6-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1-7-2008 has been entered.

The amendment and response filed on 1-7-2008 are acknowledged. Claims 1, 7, 14-15, 17 and 19 have been amended. Claim 16 has been canceled. Claim 20 has been added. Claims 1, 3, 7 and 9-15 and 17-20 are pending and currently under examination.

Information Disclosure Statement

The Information Disclosure Statements filed on 12-18-2006, 6-6-2006 (2), 1-7-2008 and 3-6-2008 have been considered. Initialed copies are attached hereto.

Declaration

The Declaration filed under 37 C.F.R. 1.131 by John C. Bell, David F. Stojdl, Harold L. Atkins and Brian D. Lichty on 1-7-2008 has been considered.

Applicant's request for the withdrawal of the finality of the Office action mailed on 12-6-2006 is noted. However, in light of the request for continued examination under 37 CFR 1.114 fled on 1-7-2008, the issue is moot.

With regard to Applicant's comments regarding the "filing dates" of papers, the dates referred to by the Examiner reflect the date a given paper was received and processed by the USPTO, not the date on which said paper was mailed.

Petition to Change Inventorship Under 37 C.F.R. 1.48(b)

Applicant's request that the inventorship of the present application be amended to delete Nahurn Sonenberg, Earl G. Brown, Ricardo M. Marius and Shane B. Knowles as inventors of the instant application is approved.

Claim Rejections Withdrawn

The provisional rejection of claims 1 and 4-6 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 and 6-9 of copending Application No. 10/717,101 is withdrawn in light of the amendment thereto.

The rejection of claims 1, 14-15 and 17 are rejected under 35 U.S.C. 102(a) as being anticipated by Roberts et al. (WO 99/18799) is withdrawn in light of the amendment thereto.

The rejection of claim 16 rejected under 35 U.S.C. 103(a) as being unpatentable over Roberts et al. (WO 99/18799 --IDS) in view of Molnar-Kimber et al. (WO99/45783 --IDS) is withdrawn in light of the declaration filed under 37 C.F.R. 1.131 by John C. Bell, David F. Stojdl, Harold L. Atkins and Brian D. Lichty on 1-7-2008.

Claim Rejections Maintained

35 USC § 112, Deposit Requirement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 9-13 under 35 U.S.C. 112, first paragraph, for failing to meet the biological deposit requirements is maintained for reasons of record.

Applicant argues:

1. A variety of researchers have had access to VSV mutant strains and therefore a deposit is not necessary.

2. Many scientific journals require their authors to agree to make biological materials available to the research community.

Applicant's arguments have been fully considered and deemed non-persuasive.

Applicant has failed to demonstrate that the VSV strains designated M1, M2, M3, M4 and M5 are well known and **readily** available to the public **without restriction**.

As outlined previously, it is apparent that the VSV strains M1, M2, M3, M4 and M5 are required in order to practice the invention. The deposit of biological organisms is considered by the Examiner to be necessary for the enablement of the current invention (see 37 CRF 1.808(a)).

If the deposit is made under terms of the Budapest Treaty, then an affidavit or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty *and* that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit, or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the following criteria have been met:

1) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

2) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent; and

3) the deposits will be maintained for a term of at least thirty (30) years from the date of the deposit or for the enforceable life of the patent or for a period of at least five (5) years after the most recent request for the furnishing of a sample of the deposited material, whichever is longest; and

4) a viability statement in accordance with the provisions of 37 CFR 1.807; and

5) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 CRF 1.809(d) should be added to the specification. See 37 CFR 1.803 – 1.809 for additional explanation of these requirements.

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 7 and 9-15 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods utilizing cells infected with attenuated VSV for reducing the viability of cell lines *in vitro* and the use of attenuated VSV to reduce the viability of tumor cell based xenographs in immunodeficient mice, does not reasonably provide enablement for the utilization of cells infected with VSV for the reduction of viability of all types of melanoma tumor cells (either *in vivo* or *in vitro)* or the utilization of said

attenuated VSV to reduce the viability of a tumor cell in an immunocompetent animal for the reasons set forth in the previous Office action in the rejection of claims 1, 3, 7 and 9-19.

Applicant argues:

1. There is no limitation to "treat cancer" in the instant claims.

2. The BPAI decisions in *Ex parte* Boutin and *Ex parte* Saito and Zhao both stand for the proposition that unless the claims explicitly refer to a therapeutic benefit, typically, the examiner should not determine if the claims are enabled for an unclaimed therapeutic benefit. The clinical response is not pertinent for meeting the enablement requirement with regard to the claimed invention

Applicant's arguments have been fully considered and deemed non-persuasive.

Contrary to applicant's assertion, the reduction in the viability of a tumor cell in the context of a living being (i.e. *in vivo* applications) constitutes a therapeutic response. Moreover, the BPAI decisions in *Ex parte* Boutin and *Ex parte* Saito and Zhao are not germane to the instant application as the fact patterns are different.(i.e. the instant claims refer to a therapeutic response). Consequently, clinical response is pertinent with regard to the enablement of the instant claims.

As outlined previously, enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to methods of reducing the viability of melanoma tumor cells by administering cells infected with VSV to said melanoma tumor cells. Said melanoma tumor cells can optionally have no PKR activity and/or have no STAT1 activity (claim 3). Said VSV virus can be unable to inactivate tumor cell PKR activity (claims 7 and 18), or may constitute strains M1-M5 (claims 9-13, respectively). Said method may be drawn to methods of "treating" tumor cells which reside in a mammalian host (claims 14-15 and 20). Said infected cells may be administered with the optional administration of interferon prior to the administration of the virus (claim 19).

Breadth of the claims: The claims are extremely broad in that they encompass literally any VSV strain. Moreover, claims 14-15 and 20 are specifically drawn to the *in vivo* application of the claimed methods (i.e. treatment of a melanoma tumor cell within an animal) while claims 1, 3, 7, 9-15 and 17-20 encompass both *in vivo* and *in vitro* applications. It should be noted that all the instant claims (except claim 20) read on the *in vivo* treatment of melanoma tumor cells in humans.

Guidance of the specification/The existence of working examples: To use the invention as claimed one must be able to differentially infect a susceptible tumor cell resulting in a reduction in said cell's viability. The specification provides great detail on the susceptibility of different cell types to VSV and the protective effect of alpha interferon against VSV infection. However, the instant claims are drawn to all forms of melanoma tumor cells, while the specification has demonstrated only a single melanoma cell line (SK-MEL3) that is susceptible to VSV infection. (see Table 1 and page 28 of the specification) and said melanoma cell line was shown to be rapidly destroyed by VSV infection *in vitro* (see Table 2 and page 28 of the specification). The specification is silent on what receptor is utilized by VSV for cell entry or which cell types would be able to support a productive viral infection making it difficult to determine if a given tumor cell would be susceptible to the oncolytic properties of VSV or be used as a suitable delivery vehicle. Moreover, the specification is equally silent on what other melanoma tumor cell types are killed by VSV infection. The invention seems to be predicated on the susceptible tumor cells lacking PKR activity, but the specification is silent on which melanoma tumor cells lack said function. Claims 14-15 and 20 are specifically drawn to the *in*

vivo application of the claimed methods while claims 1, 3, 7, 9-15 and 17-20 encompass both in *vivo* and *in vitro* applications.

State of the art: At the time of applicants' invention the art of using oncolytic viruses to treat melanomas was underdeveloped. While the use of oncolytic viruses has been known in the art for decades, said oncolytic viruses were limited, to viruses that would be considered human pathogens.

Predictability of the art and the amount of experimentation necessary:

People of skill in the art require evidence that a benefit can be derived by the therapeutic application of a given substance; however, a survey of the relevant art does not indicate that substances such as those claimed provide such benefit. The instant specification fails to provide significant direction on which viruses, if any, are capable of eliciting a therapeutic response (tumor cell death) when administered to an immunocompetent subject in need. Moreover, the specification is equally silent on how said viruses are to be administered to said subject. Jain discloses known barriers to the delivery of drugs into solid tumors (Scientific American Vol. 271 No. 1, pages 58-65, July 1994). Impediments to drug delivery include: (1) Non-uniform blood delivery to all areas of the rumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61) and (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1). Consequently, the method of administration would vary depending on the tumor cell type and location of said tumor. Unfortunately, the specification fails to provide guidance to

how a given virus should be administered when treating a given carcinoma. The specification illustrates this point on page 33 where it states that PKR-/- mice were killed with VSV by several routes of infection but that these mice were not affected by intravenous injections of the virus. Moreover, there is a marked difference in the efficacy of delivering a therapeutic agent to a solid tumor cell as opposed to a leukemia cell.

The specification teaches how to use VSV to reduce the viability of melanoma cell lines injected into immunodeficient mice to form xenographs and provides *in vitro* data showing effects of VSV infection on a single melanoma cell line (either with or without alpha interferon). However, the specification does not provide any basis for correlating the *in vitro* results with beneficial effects that could reasonably be expected when said viruses are administered *in vivo* to "treat" carcinoma tumor cells, although *in vivo* use is clearly encompassed by the claims. Lacking either direct evidence for *in vivo* benefit, or a reasonable basis for correlating the *in vitro* and xenograft data as exemplified in the instant specification with *in vivo* benefit. Hence, the specification cannot be said to teach how to use the claimed viruses as pharmaceuticals without undue experimentation. Moreover, while those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are somewhat useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to *in vivo* efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time,

lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro)*. Moreover, Dermer (Bio/Technology, 1994, Vol. 12 page 320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature 'for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Additionally, it should be noted that Example 25 is insufficient to provide enablement for the full breadth of the instant claims. Firstly, the xenographs utilized in Example 25 (on page 50

of the specification), comprise a melanoma derived cell line (SK-MEL3). Secondly, said example only utilizes two of the five VSV mutants disclosed in the instant specification suggesting that the anti-tumor effect of the disclosed VSV mutants is unpredictable. Thirdly, the instant claims are drawn to use of VSV to reduce the viability of all types of melanoma tumor cells whereas Example 25 demonstrates only that two mutated VSV viruses can reduce the viability of cell-line based xenographs in immunodeficient mice. This cannot be extrapolated to the use of wild-type (non-mutated) VSV against established tumors in an immunocompetent animal. Gura (Science, Vol. 278, 1997 pages 1041-1042) teach that xenographs are not good models for determining the efficacy of a treatment modality since "xenograft tumors don't behave like naturally occurring tumors in humans" (see column 2). Gura illustrates the lack of correlation between efficacy in xenograft model systems and in vivo efficacy in humans when she states that the use of xenografts led them to discover "compounds that were good mouse drugs rather than good human drugs" (see the bottom of column 2 on page 1041).

Consequently, the specification while being enabling for methods utilizing VSV for reducing the viability of cell lines *in vitro* and the use of VSV to reduce the viability of tumor cell based xenografts in immunodeficient mice, does not reasonably provide enablement for the utilization VSV for the reduction of viability of all types of melanoma tumor cells (either *in vivo* or *in vitro)* or the utilization of any virus to reduce the viability of a melanoma tumor cell in an immunocompetent animal. The specification does not enable any person of skill in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Additionally, on the basis of experimentation performed using an animal model, the specification asserts the invention can be used to treat cancer (melanoma). The problem with accepting such an assertion lies in the fact that the data generated using such mouse models cannot be reasonably extrapolated to reliably and accurately predict whether the claimed invention can be used to attenuate at least a substantial number of pathoangiogenic conditions comprising cancer and furthermore, as of yet, the clinical, therapeutic application of cancer "vaccines" to attenuate cancer has been met with very little success. In addition to references cited in preceding Office actions, which also describe such disappointing results and attribute the lack of success to various differences, such as the poor extrapolation of promising preclinical data to predict clinical efficacy, Wang et al. (*Exp. Opin. Biol. Ther.* 2001; 1 (2): 277-290) reviews the state of the art of T-cell-directed cancer vaccines for treatment of melanoma and states:

> Saved for scattered reports, however, the success of these approaches has been limited and T-cell-directed vaccination against cancer remains at a paradoxical standstill whereby anticancer immunization can be induced but is not sufficient, in most cases, to induce tumour regression (abstract).

Wang et al. further states:

> Among the questions raised by this paradoxical observation [that systemic T-cell responses to vaccines often do not lead to objective clinical tumor regression] stands the enigma of whether tumour resistance to immunotherapy is due to insufficient immune response or because tumour cells rapidly adapt to immune pressure by switching into less immunogenic phenotypes [citations omitted].

In addition, Kelland (*Eur. J. Cancer.* 2004 Apr; **40** (6): 827-836) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). While the successful use of such models in cytotoxic drug development is conclusive, Kelland discloses that today there is far less focus on the development of such drugs (page 833, column 2); rather, the focus is upon the development of "molecularly-targeted", largely cytostatic drugs,

such as those disclosed in the instant application, which may act in synergy with other drugs to selectively reduce or inhibit the growth of neoplastic cells (e.g., page 885). In particular, where such drugs are naked humanized antibodies that act through mechanisms such as ADCC, Kelland states the models are of limited value, because such mechanisms depend upon the recruitment of the host's (i.e., mouse) immune response, which differs from or is not reflective of that found in man (page 834, column 2). With such limitations of the xenograft model in mind, Kelland suggests that the case for using the model within a target-driven drug development cascade need to be justified on a case-by-case basis (page 835, column 1). Still, Kelland et al. does not altogether discount the usefulness of such models, since, at present, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even in silico methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2). Kelland, however, does not advocate the use of a single xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not.

Moreover, as noted in preceding Office action, Gura (of record) teaches that although researchers had hoped that xenografts would prove to better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, "the results of xenograft screening turned out to be not much better than those obtained with the original models". Gura states that as a result of their efforts, " '[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs' ".

With further regard to the predictive value of various different preclinical models, Voskoglou-Nomikos et al. (*Clin. Cancer Res.* 2003 Sep 15; 9: 4227-4239) reports in a retrospective analysis that mouse allograft models were not predictive and xenograft models were only predictive for non-small cell lung and ovarian cancers, but not for breast or colon cancers; see entire document (e.g., the abstract).

Finally, Saijo et al. (*Cancer Sci.* 2004 Oct; **95** (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Applicant has argued that the use of xenografts in mice for evaluating therapeutic efficacy of drugs for treating humans is well established; agreeably the model has been utilized, but its use should not be considered sufficient to show that the claimed invention can be used without undue or unreasonable experimentation because of the poor extrapolation of the results to accurately and reliably predict the effectiveness of treating humans with the same agent or regimen. Schuh (*Toxicologic Pathology*. 2004; **32** (Suppl. 1): 53-66) reviews the trials, tribulations and trends in tumor modeling in mice to disclose, for example, that "[c]ommon reliance on survival and tumor burden data in a single mouse model often skews expectations

towards high remission and cure results; a finding seldom duplicated in clinical trials" (abstract). Furthermore, Schuh discloses, "[d]espite historical significance and ongoing utility, tumor models in mice used for preclinical therapeutic intervention often error towards false positive results and curing cancer in mice" (page 62, column 1). Given the noted limitations of xenograft models, Schuh suggests that testing in tumor-bearing animals may help to improve the predictive value of animal modeling; see entire document (e.g., the abstract).

Bibby (*Eur. J. Cancer.* 2004 Apr; **40** (6): 852-857) teaches that in the interest of finding more clinically relevant models, orthotropic models have been developed; see entire document (e.g., the abstract). In such "orthotopic" models, treatment is initiated after removal of the primary tumor and distant metastases are well established and macroscopic. These models have their advantages, but the procedures involved in using such models are far more difficult and time-consuming than conventional subcutaneous (e.g., xenograft) models; see, e.g., page 855, column 2.

The position of the Office is further substantiated by the teachings of Peterson et al. (*Eur. J. Cancer.* 2004; **40**: 837-844). Peterson et al. teaches numerous agents have show exciting activity in preclinical models and yet have had minimal activity clinically; see, e.g., the abstract. Such disappointments, Peterson et al. discloses, "have led to reasonable skeptism about the true value of both syngeneic and xenograft rodent tumour models in accurately identifying agents that will have important clinical utility" (abstract). Peterson et al. reviews the limitations of the xenograft models; see entire document (e.g., page 840, column 2).

Thus, taken collectively, there is a preponderance of factual evidence of record that the showing provided in the supporting disclosure would not enable the skilled artisan to practice the

claimed invention without undue experimentation, as required under the provisions of 35 U.S.C. § 112, first paragraph.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 7, 14-15 and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roberts et al. (WO 99/18799 – IDS) in view of Coukos et al. (Clinical Cancer Research, 1999, Vol. 5, pages 1523-1537 – IDS filed on 1-7-2008).

Roberts et al. disclose methods utilizing oncolytic viruses to treat (kill) neoplasms wherein said treatment comprises contacting the neoplastic tumor cells with the virus (see abstract). Roberts et al. further disclose that the oncolytic virus can be vesicular stomatitis virus (see page 21 and Table 1) and that VSV was capable of tumor cell specific killing (i.e. VSV selectively infects tumor cells deficient in IFN responsiveness and not "normal" cells)[see page 26, first paragraph]. Moreover, Roberts et al. disclose that their methods could be used to treat melanomas (see page 30, last paragraph).

Roberts et al. differ from instant invention in that they do not disclose the use of cells (i.e. producer cells) for the delivery of the oncolytic virus.

Coukos et al. disclose the use of producer cells for the delivery of oncolytic HSV-1 to tumor cells (see abstract). Moreover, Coukos et al. disclose that the use of producer cells may have many advantages over direct injection methods. Said advantages include: 1) amplification of viral load; 2) delivery of a virus within a producer cell may enable the virus to elude the subjects immune system; 3) use of producer cells with a binding affinity for the tumor cells would increase the localization of virus delivery; and 4) a vaccine antitumor response in selective patients might be generated (see page 1536).

Consequently, it would have been obvious to one of skill in the art to use producer cells, as disclosed by Coukos et al., in the method of melanoma tumor cell treatment disclosed by Roberts et al. One would have been motivated to due so in order to receive the benefits associated with the use of producer cells, as disclosed by Coukos et al. and cited above. One of ordinary skill in the art would necessarily have a reasonable expectation of success since both methods utilize oncolytic viruses to treat tumor cells. Moreover, given the success of using carrier cells to deliver

oncolytic HAV-1, it would have been obvious for the skilled artisan to try and adapt said system to other oncolytic virus (e.g. VSV) types. Finally, given that the use of VSV as a cancer treatment is well known in the art yielding predictable results, it is obvious for the skilled artisan to use the VSV of Roberts et al. (see *KSR International Co. v. Teleflex Inc.*, No. 04-1350 [U.S. Apr. 30, 2007]).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT A. ZEMAN whose telephone number is (571)272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m. .

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Robert A. Zeman/
Primary Examiner, Art Unit 1645
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